REMARKS

Claim Amendments:

Claims 1, 20, 21 and 70 have been amended to limit the claimed antigen to a tumor antigen. This amendment is supported by prior Claim 72 (now cancelled) and by the specification on page 22, lines 15-16. Claims 12, 71 and 72 have been cancelled without prejudice to or disclaimer of the subject matter therein. These amendments merely cancel claims or place the claims in a better condition for consideration on appeal, and Applicants submit that the claims are in a condition for allowance. The Examiner's consideration of the same is respectfully requested.

Declaration of Geoffrey Pietersz

Applicants submit herewith a new Declaration under 37 CFR 1.132 of Dr. Pietersz. This Declaration is essentially a "Supplemental Declaration" in that it is a resubmission of the prior Declaration filed on December 18, 2002, except that the issues raised by the Examiner in the April 26 Office Action have been clarified for the record by Dr. Pietersz. This Declaration was not previously submitted in its current form because Applicants and Dr. Pietersz had believed that the prior Declaration was clear and sufficient to present the data. Moreover, this Declaration is submitted only to clarify issues that were raised by the Examiner in response to the first submission of the Declaration. It is believed that this Declaration and the accompanying remarks below address most of the Examiner's final issues and therefore, consideration of this Declaration after final rejection is respectfully requested in the interest of expediting prosecution.

Objection to the Specification and Rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70-72 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has maintained the prior rejection of claims under 35 U.S.C. § 112, first paragraph, on the basis of enablement. The Examiner acknowledges that the specification is enabling for immunoregulatory compositions comprising mannose-receptor bearing cells and a conjugate comprising MUC1 and a carbohydrate polymer comprising mannose, wherein the carbohydrate polymer is a fully oxidized carbohydrate polymer comprising free aldehydes. However, the Examiner contends that the specification is not enabling for any antigen as a component of the claimed composition.

Initially, Applicants note that the claims have been amended to expedite prosecution, by claiming only tumor antigens, rather than any antigen. Applicants have provided evidence of the *in vivo* efficacy of the claimed composition using *two different mannose receptor bearing cells*, namely, macrophages (see Examples in specification) and dendritic cells (see December 18 or current Declaration under 37 CFR 1.132 of Dr. Pietersz), and *two different tumor antigens*: mucin, as described in the Examples of the specification, and CRIPTO, which was presented in a Declaration of Geoffrey Pietersz on December 18, 2002 and in the current supplement to that Declaration. Applicants understand that the Examiner has some questions regarding the data from the Pietersz Declaration and Applicants' prior arguments and have tried to address these issues below.

Davis et al.

In the April 26 Office Action, the Examiner first refers to Applicants' prior arguments (summarized in points 1-3 and 7 on page 3 of the April 26 Office Action), and contends that Applicants' arguments and the publication of Davis et al. demonstrate the effects of antigen-conjugate only, reminding Applicants that the mannose receptor bearing cells are part of the claimed composition.

In response to this point, Applicants first refer to Davis et al. and note that this publication describes the pulsing of macrophages with a conjugate comprising oxidized mannan and a parasitic antigen. As taught by the present specification (e.g., see page 15, line 21; page 16, lines 1-3; page 19, lines 5-9; Example 1 and Table 1), a macrophage is a mannose receptor bearing cell and therefore, the experiment in Davis et al. is commensurate in scope with the claimed composition, as Davis et al. contacts these mannose receptor-bearing cells with the oxidized mannan-parasitic antigen conjugate to form the composition of the invention as previously claimed, and then measures the cytokine production by the macrophages as an indicator of a microenvironment conducive to the stimulation of T cell responses. Therefore, the Davis et al. publication is indeed relevant to the issue of the predictability of use of the composition with any antigen. Nonetheless, as discussed above, Applicants have limited the present claims to recite a tumor antigen.

Declaration of Dr. Pietersz under 37 CFR 1.132

The Examiner has also questioned the data presented previously in the Pietersz Declaration. Specifically, the Examiner contends that the Declaration was not clear with regard to whether the mannose portion of the conjugate was oxidized or not because the specification describes both

oxidized and partially reduced mannose. The Examiner has also stated that the CRIPTO data provided in the Declaration is not commensurate in scope with the claimed invention because the data shows *ex vivo* pulsing of dendritic cells with CRIPTO, and that the antigen-polymer conjugate was removed from the dendritic cells prior to administration to mice.

In response to the issue regarding oxidized mannose, Applicants submit herewith the Declaration of Geoffrey Pietersz under 37 CFR 1.132 which, as discussed above, is effectively a supplement to the prior submitted Declaration that attempts to clarify the experimental data for the Examiner. First, as now clearly stated in paragraph 4 of the Declaration, the experiments using the antigen, CRIPTO, were conducted by preparing an antigen-polymer conjugate wherein the mannose was *oxidized*. The conjugate was prepared using essentially the same basic protocol as used for the oxidized-mannan-MUC1 conjugate in the specification, and therefore, the CRIPTO conjugate also meets the limitation of including a fully oxidized carbohydrate polymer comprising free aldehydes.

Second, with regard to the Examiner's contention that the data do not demonstrate a composition that is commensurate in scope with the claims, Applicants respectfully disagree. The composition as presently and previously claimed comprises: "isolated mannose receptor-bearing cells and a conjugate comprising a [tumor] antigen and a carbohydrate polymer comprising mannose, wherein said carbohydrate polymer is a fully oxidized carbohydrate polymer comprising free aldehydes". Applicants believe that the Examiner may not be considering exactly how the composition of the present invention operates and has therefore overlooked the fact that the composition set forth in the Declaration corresponds directly to what is claimed. More particularly, the reason for including the mannose receptor bearing cells in the composition is that the mannose portion of the conjugate binds to the mannose receptors on the cells, and can then be internalized, whereby the attached antigen is processed and presented by the cells to significantly enhance the immune response against the antigen. The advantages of this composition are set forth, for example, in the Summary of the specification. Furthermore, the specification is clear on this point, as set forth on page 12, line 14 to page 13, line 4 of the specification:

> According to the present invention, reference to a composition comprising "carbohydrate receptor-bearing cells and a conjugate comprising an antigen and oxidized carbohydrate" or "carbohydrate receptor-bearing cells contacted with a conjugate comprising an antigen and oxidized carbohydrate" can encompass one or

more of: (1) a mixture of conjugate and receptor-bearing cells wherein the conjugate is not bound to the cells; (2) a mixture of conjugate and receptor-bearing cells wherein the conjugate is bound to the cells, but not yet internalized; (3) receptor-bearing cells wherein the conjugate has been internalized; (4) receptor-bearing cells wherein the conjugate has been internalized and processed; and/or (5) receptor-bearing cells wherein the conjugate has been internalized, processed and presented.

Therefore, in the case of the "washing step" referenced in the Declaration and of concern to the Examiner, only free (unbound) conjugate would have been washed away. The composition that was administered to the mice still comprises both the conjugate and the mannose receptor bearing cells, because the conjugate, after being contacted with (combined with, pulsed with) the mannose receptor bearing cells, will bind to the cells via the mannose receptors, and then at least some of the conjugate will have been internalized by the cells for processing after 2 hours of pulsing (e.g., scenarios (2)-(4) in the quotation from the specification above). As stated in the specification and as previously argued by Applicants, among the advantages of the present composition are the ability of the conjugate to avoid recognition by naturally occurring antibodies *in vivo* and even more importantly, the ability of the conjugate to be delivered to the MHC Class I pathway for significant enhancement of T cell responses against the antigen. Washing away from the composition of any excess free, unbound conjugate can further enhance these advantages by reducing the likelihood of free conjugate cross-reacting with the naturally occurring antibodies *in vivo* (e.g., Gal). These advantages are achieved by the special components of the invention in combination. These advantages do not need to be recited in the claims as they are inherent features of the combining of the recited mannose receptor bearing cells with the recited antigen conjugate that includes mannose, wherein the carbohydrate polymer is a fully oxidized carbohydrate polymer comprising free aldehydes (i.e., the mechanism by which the composition operates illustrates the advantages of the invention).

The claimed invention is a composition that has been demonstrated first in the specification by working examples using one combination of mannose receptor bearing cell (macrophage) and a tumor antigen (MUC1), and again using a different mannose receptor bearing cell type (dendritic cell) and different tumor antigen (Cripto) in the Declaration of Dr. Pietersz. In both the specification and the Declaration, *in vivo* efficacy using the claimed composition was demonstrated. The claims do not require that the components of the composition be separate from one another, as the Examiner

seems to imply, and indeed, once combined into a composition as claimed, the components will begin to associate with one another via the binding of the mannose component to the mannose receptors on the cells.

Therefore, Applicants submit that the composition set forth in the present claims, as amended, are fully enabled by the specification, as evidenced by the additional experimental data provided by Dr. Pietersz Declaration. In view of these remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70-72 under 35 U.S.C. § 112, first paragraph.

Objection to the Claims:

The Examiner has objected to Claim 71 as being a substantial duplicate of Claim 70. To expedite prosecution, Applicants have cancelled Claim 71 without prejudice to or disclaimer of the subject matter therein.

Applicants have attempted to respond to all of the issues raised by the Examiner in the April 16, 2004 Office Action, and in a manner in accordance with 37 CFR 1.116. Therefore, Applicants submit that the claims are in a condition for allowance and respectfully request that if the Examiner has any further concerns with regard to the claims, that he consider contacting the below-named agent at (303) 863-9700 to expedite prosecution.

Respectfully submitted,

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